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Title: COST-EFFECTIVENESS OF UNIVERSAL HEPATITIS C VIRUS SCREENING OF PREGNANT WOMEN IN THE UNITED STATES

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Running title: HCV screening of pregnant women

Brief Summary. Despite increases in hepatitis C virus (HCV) among pregnant women, the Society of Maternal-Fetal medicine only recommends risk-based screening. We find HCV screening among pregnant women in the U.S. is cost effective and should be recommended nationally by all societies.

ABSTRACT

Background: Hepatitis C Virus (HCV) chronic prevalence among pregnant women in the United States (U.S.) U.S. doubled nationally from 2009-2014 (~0.7%), yet many remain undiagnosed. Screening pregnant women is not recommended by the Society of Maternal-Fetal Medicine or the Centers for Disease Control and Prevention, despite new AASLD/IDSA guidelines recommending screening this group. We assessed the cost-effectiveness of HCV screening for pregnant women in the U.S.

Methods: An HCV natural history Markov model was used to evaluate the cost-effectiveness of universal HCV screening of pregnant women followed by treatment after pregnancy compared to background risk-based screening from a health care payer perspective. We assumed 0.73% HCV chronic prevalence among pregnant women based on national data. We assume no Medicaid reimbursement restrictions by fibrosis stage at baseline, but explore differing restrictions in sensitivity analyses. We assessed cost (in USD\$) and health outcomes (in quality-adjusted life years, QALYs) over a lifetime horizon, using new HCV drug costs of \$25,000/treatment. We assess mean incremental cost-effectiveness ratios (ICERs) under a willingness to pay threshold of \$50,000/QALY gained. We additionally evaluate potential population impact.

Results: Universal antenatal screening was cost-effective in all treatment eligibility scenarios (mean ICER <\$3,000/QALY gained). Screening remained cost-effective at 0.07% prevalence, the lowest estimated prevalence state in the U.S. (Hawaii). Screening the ~5.04 million pregnant women in 2018 could result in detection and treatment of 33,000 women based on current fibrosis restrictions.

Conclusions: Universal screening for HCV among pregnant women in the U.S. is cost effective and should be recommended nationally.

Key words: testing, hepatitis c virus, economic, treatment, antenatal, pregnancy

INTRODUCTION

Hepatitis C virus (HCV) infection among pregnant women doubled in the United States (U.S.) from 2009-2014, reaching 8% in rural Tennessee.(1) Roughly 0.7% of pregnant women have chronic HCV infection in the U.S.(2), equating to ~42,000 pregnancies and 29,000 births among HCV-infected women annually. Despite the availability of highly-effective (>90% cure) HCV direct-acting antivirals (DAAs)(3), the majority of these women remain undiagnosed and unlinked to care.

Currently, there is disagreement about HCV screening among pregnant women in U.S. clinical guidelines. Recent Society of Maternal-Fetal Medicine (SMFM) and American College of Obstetrics and Gynecology (ACOG) guidelines reaffirmed recommendations for risk-based testing only for HCV among pregnant women.(4) Similarly, the U.S. Center for Disease Control (CDC) recommends routine screening for HIV, hepatitis B virus, and syphilis, but not for HCV among pregnant women.(5) By contrast, recent AASLD/IDSA guidelines recommend HCV screening for all pregnant women, ideally at the initiation of prenatal care.(6) Additionally, in April 2018, the Kentucky legislature recommended testing pregnant women due to high burden in that state.(7) For many women, pregnancy is one of their few contact points with health care, and a time of health insurance coverage, and as such pregnancy could provide a critical opportunity for reaching this population. To our knowledge, no study has evaluated the cost-effectiveness of HCV screening in pregnant women in the DAA era in the U.S.

To inform HCV screening policy and practice, we assessed the cost-effectiveness of universal HCV screening among pregnant women in the U.S., followed by treatment after pregnancy as determined by state-based Medicaid fibrosis restrictions.

METHOD

Overview: We performed a cost-effectiveness analysis of universal HCV screening among pregnant women in the U.S. compared to background risk-based screening from a public sector health care payer perspective. Our cost-effectiveness analysis includes long-term health benefits among pregnant women only, but we additionally examine potential impact in terms of HCV diagnoses among children born to HCV infected mothers in the “Estimation of Impact” section.

Baseline and comparator: We explored the cost-effectiveness of HCV antenatal screening followed by treatment after pregnancy compared to background risk based screening. Our main analysis explores the cost-effectiveness in a setting with no treatment restrictions by fibrosis stage but we additionally explore scenarios with differing treatment eligibility (see sensitivity analyses).

Model. We utilized a deterministic HCV natural history closed cohort Markov model of HCV disease progression and treatment among pregnant women attending antenatal clinics (**Figure S1**). The population was stratified by HCV infection stage, and HCV diagnosis and follow-up status. We assumed all individuals become diagnosed and under follow-up upon progression to decompensated cirrhosis or hepatocellular carcinoma due to clinical severity. We incorporate loss-to-follow-up among diagnosed women; individuals lost to follow-up were eligible for retesting in the community. Individuals who attained SVR with METAVIR F3 or lower were assumed not to progress further for HCV, whereas those with F4 or beyond progress at a lower rate compared to their HCV-infected counterparts. Individuals whose treatment failed were not retreated.

Cost-effectiveness methods. Cost (in 2018 USD \$) and health utilities (in quality-adjusted life years, QALYs) were attached to each health state and discounted 3%/year. Due to parameter uncertainty, we

performed a probabilistic uncertainty analysis where parameters were randomly sampled from probabilistic distributions (**Table 1**) to generate 10,000 parameter sets. For each parameter set, the model was run and outputs generated. We calculated the mean incremental cost-effectiveness ratios (ICER, \$/QALY gained, mean incremental costs divided by the mean incremental QALYs) for the antenatal screening compared to background risk-based screening for each treatment eligibility scenario, assessing cost-effectiveness under a willingness to pay threshold of \$50,000/QALY gained.(8)

Sensitivity Analyses on Cost-effectiveness Results. Due to state differences in Medicaid reimbursement policies by fibrosis stage, we additionally examine scenarios where treatment is restricted until an individual reaches METAVIR stage F1 or beyond (F1+), METAVIR stage F2 or beyond (F2+), METAVIR stage F3 or beyond (F3+), each compared to background screening. In these restriction scenarios, women with chronic HCV infection are eligible for treatment upon progression to these disease stages if they remain linked to care.

Additionally, for each treatment eligibility scenario, we perform numerous one-way sensitivity analyses. Due to state variability in HCV chronic prevalence among pregnant women(1), we examined the impact of varying HCV prevalence. We additionally performed one-way sensitivity analyses to examine how the ICER changed with alterations in: SVR (85% and 95% versus 90% at baseline), age at pregnancy (22 or 32 compared to 27 at baseline), HCV treatment costs (\$75,000 versus \$25,000 at baseline), HCV treatment delivery costs (\$625 USD versus \$1,249 at baseline), proportion previously diagnosed and under follow-up (40% compared to 18% at baseline), discount rate (0% for costs and health utilities, or 3% for utilities and 6% for costs, versus 3% for each at baseline), liver transplantation costs (50% or 200% baseline costs), loss-to-follow up rate per year (10/30/50% per year compared to 12% at baseline), background testing rate (10% or 0% per year, compared to 5% at baseline), baseline fibrosis stage distribution (3% cirrhosis versus 10% at baseline) and HCV screening uptake (85% based on HBV testing uptake among pregnant women, compared to 100% at baseline).(9) Additionally, our baseline fibrosis progression rate among U.S. women produced 15% cirrhosis or more advanced liver disease at 20 years, but a recent publication among a German cohort found lower rates of progression (21% cirrhosis or further

at 35 years for treatment naïve women(10)), so we evaluated a scenario with lower fibrosis progression rates.

Estimation of U.S. Population Impact: We additionally estimated the national impact of implementing HCV screening of pregnant women in 2018. Due to state heterogeneity in fibrosis restrictions, we first generated state-level estimates of the number of pregnant women in a given year (number of births + number of fetal losses + number of abortions). (11-13) We estimated births and abortions by multiplying the number of women aged 15-44 in a given state by the state-specific birth rate and abortion rate, respectively. We estimated fetal losses using the national fetal loss rate based on CDC recommendations due to state-level differences in fetal loss reporting by gestational age.(11) As 2016 estimates indicate only 1.6% of women do not access any prenatal care during pregnancy, we assumed for simplicity all women are eligible for screening (14). Based on state-level estimates of pregnant women in 2018 and state fibrosis restriction(15), we multiplied the number of pregnant women by HCV identification and treatment rates generated from the economic model for each fibrosis restriction scenario assuming the national HCV prevalence among pregnant women. We summed state-level estimates to generate a national estimate of the total and incremental number of pregnant women identified and treated with HCV antenatal screening. We also estimated the total and incremental number of HCV-infected children born who would be identified through follow-up screening based on maternal diagnosis during pregnancy. For this analysis, we assumed a vertical HCV transmission rate of 5.8% from a recent meta-analysis.(16) Follow-up testing rates among children born to HCV-infected mothers are uncertain, but a recent study(17) found few (16%) children born to known HCV-infected mothers were tested at 18 months as recommended by AASLD and pediatric societies(6), so we assumed 16% for this analysis.

Model Parameterization:

All model parameters and sampling distributions are presented in **Table 1**.

Baseline Population Characteristics. The baseline population included pregnant women with an average age of 27 years (based on the median age of reproductive-aged women in the U.S.).(2) We assumed a chronic HCV prevalence among pregnant women of 0.73% (95%CI: 0.71-0.75%) based on national estimates(2), corresponding to an anti-HCV prevalence of 1.11%, given 34% spontaneous clearance in women.(9) We assumed a chronic HCV prevalence among people who inject drugs (PWID) of 52% (range 43-60%) based on national estimates.(18, 19) HCV fibrosis distribution was based on U.S. national estimates for women.(20)

Estimates of the proportion of HCV-infected pregnant women diagnosed and currently under follow-up for HCV are unknown. The 2008 NHANES survey estimated 50% of HCV-infected individuals were diagnosed, but this was lower among young individuals (29% for age <40).(21) Updated estimates indicate the overall proportion diagnosed has increased by a relative 10% (from 50% in 2008 to 55% in 2017).(22) Based on this, we assumed 32% of pregnant women are currently diagnosed based on estimates among individuals age <40 (29% in 2008, estimated increase by relative 10% in 2017). We note that one study among HCV-infected pregnant women on opiate substitution therapy (OST) found 70% were previously diagnosed, but it is likely this would overestimate the proportion of all HCV-infected women diagnosed, and unclear how many were under follow-up.(23) Linkage to HCV care rates similarly vary, with recent estimates of 34% linkage within 6 months among individuals on OST(24) and 55% among patients receiving care in an outpatient clinic.(25) For this analysis, we estimated 18% of infections among pregnant women were diagnosed and linked (32% diagnosedx55% linked). We assumed 12%/year loss to follow-up after diagnosis based on data from pregnant women on OST.(26)

Disease Stage Transition Probabilities and Costs. Estimates of stage-specific transition rates among women were obtained from published studies.(27) Background (non-hepatitis C related) mortality was time-varying, based on age-specific mortality rates obtained from WHO life tables.(28) Individuals with F0-F3 fibrosis stages who achieved SVR were assumed to have no further disease progression, while individuals

with cirrhosis or more advanced disease who achieved SVR could progress at a reduced rate (**Table 1**). (29, 30) We incorporated HCV disease-related costs from published literature. (31-33)

HCV testing costs: We incorporated costs of anti-HCV and HCV RNA confirmatory testing based on the 2018 National Fee Schedule. (34) We assume individuals are screened first for anti-HCV, and if found positive are then screened for HCV RNA. Outpatient visit consultation costs were included for each testing visit. (35) For individuals who are RNA positive, we incorporate liver elastography costs for disease staging.

HCV treatment efficacy and costs: We assumed a baseline direct-acting antiviral (DAA) treatment efficacy (i.e. rate of sustained virological response [SVR]) of 90% for all genotypes. (3) We assumed drug costs for DAAs of \$25,000 per treatment course (based on the wholesale acquisition cost of glecaprevir/pibrentasvir and the price of generic sofosbuvir/ledipasvir and sofosbuvir/velpatasvir available in January 2019). (36) Cost components of treatment delivery (pre-treatment and on-treatment monitoring) were based upon the IDSA guidelines (3) and the 2018 Clinical Diagnostic Laboratory Fee Schedule (34) (**Appendix Table S1**).

Utilities. Health utilities (in quality adjusted life-years, QALYs) were obtained from previous published studies (37-39). Consistent with other analyses, we assumed a 0.05 incremental increase in health utility for patients who achieved SVR (40).

RESULTS

Cost-effectiveness: Universal HCV screening for pregnant woman was associated with incremental costs of \$53.2 (95%I -102-174) and incremental increase in QALYs of 0.019 (95%I 0.010-0.028) per pregnant woman screened compared to background risk-based screening (**Table 2**). HCV screening for pregnant women with no treatment reimbursement restrictions was cost-effective compared to risk-based screening,

with a mean ICER \$2,826 per QALY gained, and fell below the willingness to pay (WTP) threshold of \$50,000 per QALY, gained for 100% of simulations.

Screening remained cost-effective for all the alternative treatment eligibility scenarios by fibrosis stage (mean ICERs of \$1,934 \$2,026, \$2,632 in the METAVIR stage F3+, F2+, and F1+ scenarios, respectively, **Table 2**).

Screening remained cost-effective for chronic HCV prevalences among pregnant women at or above 0.03-0.04%, varying by treatment eligibility scenario (**Figure 1, Appendix Figure S2**). Results were robust to all sensitivity analyses (**Appendix Tables S2-S5**). Screening remained cost-effective in all settings with lower fibrosis progression rates (21% cirrhosis at 35 years), SVR (85%), higher proportion diagnosed and linked at baseline (40%), lower liver transplantation costs (\$112,000 per transplant), higher loss to follow-up rates (50%/year), higher background testing rates (20%/year), and lower proportion of cirrhosis in the baseline cohort (3%).

U.S. Population Impact: Given current state-by-state fibrosis restrictions, we estimate screening of the estimated 5.04 million pregnant women in 2018 would result in detection of and treatment of approximately 33,000 women overall, and an incremental detection and treatment of approximately 7,000 women, with the remainder diagnosed and treated later on in their disease. Screening could additionally result in detection of and treatment of an estimated 300 children born to mothers infected by HCV, and potentially many more if rates of return for 18 month HCV testing for children born to HCV-infected mothers increases from the currently observed 16%.

DISCUSSION

Our analysis indicates that universal HCV screening among pregnant woman in the U.S. is highly cost-effective and would be associated with improved detection of HCV among women and their children. Our results were robust to variations in state restrictions on reimbursement for HCV treatment. They were additionally robust to variations in HCV prevalence; screening pregnant women is likely cost-effective in settings with chronic HCV prevalence as low as 0.04%. Comprehensive state-specific data on HCV prevalence among pregnant women are unavailable, but it appears likely all are above this threshold. Among states reporting maternal HCV infection on infant birth certificates, HCV rates vary substantially by state, with the highest at 2.2 per 100 births in Tennessee and the lowest reported was 0.07 per 100 births in Hawaii in 2014.(1) If these data are representative of true HCV prevalence among pregnant women, screening in the lowest prevalence state (Hawaii) would remain cost-effective.(1) As such, our results support calls for a change of SMFM/ACOG and CDC guidelines to recommend universal HCV screening of pregnant women (41). Our results also provide additional economic evidence in support of the updated AASLD/IDSA guidelines(6) and Kentucky legislation(7) recommending screening pregnant women.

To our knowledge, our study is the first to evaluate the cost-effectiveness of HCV screening among pregnant women in the U.S. Our findings conflict with a previous study which found HCV screening among pregnant women in the United States not cost-effective,(42) but that study utilized old interferon-based treatments with low cure rates. Our findings are consistent with a recent study founding antenatal screening in the UK cost-effective with newer interferon-based therapies(43). Our findings are also consistent with studies finding HCV screening in the DAA era cost-effective among a variety of U.S. populations such as adolescents and young adults in primary care settings(35), in prisons(44), in methadone programs(24), and one-time testing strategies in the general population.(45) We note that our results show that screening is highly cost-effective (ICER <\$3,000), lower than previous analyses primarily because we used new drug costs of \$25,000/treatment. When we use treatment costs similar to previous analyses, we find similar cost-effectiveness results as in a recent study examining general population screening (around \$10,000/QALY gained).(45)

As with all modeling studies, ours was limited by several factors, most notably uncertainty in the underlying data. First, there is substantial uncertainty in the proportion of pregnant women previously diagnosed and engaged in care, linkage to care rates, and loss-to-follow-up rates among this population in the DAA era. However, despite this, our sensitivity analyses indicated results were robust to uncertainty in these and other parameters.

Second, we do not simulate changing insurance eligibility over time, but note in some non-Medicaid expansion states women can lose their insurance coverage as early as 30 days after giving birth. This restriction could limit timely uptake of HCV treatment. Clinical studies are underway examining the safety and efficacy of HCV treatment during pregnancy. Treatment during pregnancy could reduce the risk of loss-to-follow-up or loss of insurance coverage after pregnancy, and potentially prevent vertical transmission. Future analyses should explore the health and economic implications of treatment during pregnancy, and should incorporate women's preferences around treatment. For example, among a recent study, only 21% of HCV-infected women reported willingness to take DAAs during pregnancy for their individual benefit, but 60% reported willingness if it reduces perinatal transmission.(46)

Third, our cost-effectiveness evaluation incorporates health benefits among pregnant women only, as the outcome of HCV diagnosis during pregnancy on subsequent testing among children is uncertain and pediatric management of HCV is changing (with studies evaluating treatment among children as young as 2). As such, for the cost-effectiveness analysis we neglect additional benefits related to HCV diagnosis and management among babies born to women identified with HCV, although we estimate screening could identify ~300 children born with HCV as a result of pregnancies in 2018. Even more impact and economic benefits could be accrued due to diagnoses of future children born to these mothers. Unfortunately, data indicate subsequent testing and follow-up rates of their babies are low among HCV-diagnosed women,(17) however this may improve in the DAA era.

Fourth, we neglect the potential risk of reinfection or population treatment as prevention benefits of treatment. It is uncertain but possible a sizeable fraction of HCV-infected pregnant women remain at risk after pregnancy. However, our previous models show in settings with 50% chronic prevalence among PWID like the U.S., early treatment of people with ongoing injecting drug use is cost-effective and prevents 0.2-0.8 infections per early treatment, despite the risk of reinfection.⁽⁴⁷⁾ As such, including reinfection and prevention benefits would likely increase the cost-effectiveness of screening.

Fifth, our estimates for population impact of screening are uncertain as they are based on state-level estimates of pregnant women and estimated impact by fibrosis state restrictions, but utilize national estimates of HCV prevalence among pregnant women, due to a lack of state-level data. State fibrosis restrictions are continually changing and will affect population impact. Additionally, heterogeneity in HCV prevalence among pregnant women by state will affect these estimates, and further epidemiological studies are warranted. Nevertheless, we believe our general results indicating the potential sizeable impact of screening are robust.

In conclusion, our study provides evidence that universal HCV screening of pregnant women in the United States is cost-effective and should be recommended nationally by all clinical societies.

Notes

Disclaimer: Gilead had no influence on the design, analysis, and content of the study.

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REFERENCES

1. Patrick SW, Bauer AM, Warren MD, Jones TF, Wester C. Hepatitis C Virus Infection Among Women Giving Birth - Tennessee and United States, 2009-2014. *MMWR Morb Mortal Wkly Rep*. 2017;66(18):470-3. Epub 2017/05/12. doi: 10.15585/mmwr.mm6618a3. PubMed PMID: 28493860; PubMed Central PMCID: PMC5657980.
2. Ly KN, Jiles RB, Teshale EH, Foster MA, Pesano RL, Holmberg SD. Hepatitis C Virus Infection Among Reproductive-Aged Women and Children in the United States, 2006 to 2014. *Ann Intern Med*. 2017;166(11):775-82. Epub 2017/05/12. doi: 10.7326/m16-2350. PubMed PMID: 28492929.
3. AASLD-IDSA. Recommendations for testing, managing, and treating hepatitis C.
4. (SMFM) SoMFM. Hepatitis C in pregnancy: screening, treatment, and management 2018 [cited 2018 11/12/2018]. Available from: <https://http://www.smfm.org/publications/248-smfm-consult-series-43-hepatitis-c-in-pregnancy-screening-treatment-and-management>.
5. Centers for Disease Control and Prevention. Pregnancy and HIV, Viral Hepatitis, STD, & TB Prevention - Screening Recommendations 2018. Available from: <https://http://www.cdc.gov/nchhstp/pregnancy/screening/index.html>.
6. American Association for the Study of Liver Diseases. Recommendation for Universal Hepatitis C Screening in Pregnancy 2018 [08/2018]. Available from: <https://http://www.hcvguidelines.org/unique-populations/pregnancy>.
7. Kentucky Legislature. AN ACT relating to screening for hepatitis C. 2018.
8. Neumann PJ, Sanders GD, Russell LB, Siegel JE, Ganiats TG. Cost-Effectiveness in Health and Medicine. 2nd edition ed. 3, editor. Oxford (NY): Oxford University Press; 2017.
9. Grebely J, Page K, Sacks-Davis R, van der Loeff MS, Rice TM, Bruneau J, et al. The effects of female sex, viral genotype, and IL28B genotype on spontaneous clearance of acute hepatitis C virus infection. *Hepatology*. 2014;59(1):109-20. Epub 2013/08/03. doi: 10.1002/hep.26639. PubMed PMID: 23908124; PubMed Central PMCID: PMC3972017.
10. Wiese M, Fischer J, Lobermann M, Gobel U, Grungreiff K, Guthoff W, et al. Evaluation of liver disease progression in the German hepatitis C virus (1b)-contaminated anti-D cohort at 35 years after infection. *Hepatology*. 2014;59(1):49-57. Epub 2013/08/10. doi: 10.1002/hep.26644. PubMed PMID: 23929603.
11. MacDorman M, Kirmeyer S. The challenge of fetal mortality. *NCHS Data Brief*. 2009;16:1-8. National Center for Health Statistics (NCHS).
12. Jatlaoui TC, Shah J, Mandel MG, J.W. K, Suchdev DB, Jamieson DJ, et al. Abortion Surveillance — United States, 2014. 2017.
13. CDC CfDCaP-NCfHS. Births: Final Data for 2016. 2016 January 31, 2018. Report No.
14. CDC CfDCaP. Timing and Adequacy of Prenatal Care in the United States, 2016. 2018 May 30, 2018. Report No.: Contract No.: 3.

15. NATIONAL VIRAL HEPATITIS ROUNDTABLE (NVHR), CENTER FOR HEALTH LAW AND POLICY INNOVATION OF HARVARD LAW SCHOOL (CHLPI). Hepatitis C: State of MEDICAID Access 2018 [08/16/2018]. Available from: <https://stateofhepc.org/>.
16. Benova L, Mohamoud YA, Calvert C, Abu-Raddad LJ. Vertical transmission of hepatitis C virus: systematic review and meta-analysis. *Clin Infect Dis*. 2014;59(6):765-73. Epub 2014/06/15. doi: 10.1093/cid/ciu447. PubMed PMID: 24928290; PubMed Central PMCID: PMC4144266.
17. Kuncio DE, Newbern EC, Johnson CC, Viner KM. Failure to Test and Identify Perinatally Infected Children Born to Hepatitis C Virus-Infected Women. *Clin Infect Dis*. 2016;62(8):980-5. Epub 2016/01/23. doi: 10.1093/cid/ciw026. PubMed PMID: 26797211.
18. Denniston MM, Jiles RB, Drobeniuc J, Klevens RM, Ward JW, McQuillan GM, et al. Chronic hepatitis C virus infection in the United States, National Health and Nutrition Examination Survey 2003 to 2010. *Ann Intern Med*. 2014;160(5):293-300. Epub 2014/04/17. doi: 10.7326/m13-1133. PubMed PMID: 24737271; PubMed Central PMCID: PMC4562398.
19. Degenhardt L, Peacock A, Colledge S, Leung J, Grebely J, Vickerman P, et al. Global prevalence of injecting drug use and sociodemographic characteristics and prevalence of HIV, HBV, and HCV in people who inject drugs: a multistage systematic review. *The Lancet Global Health*. 2017;5(12):e1192-e207. doi: 10.1016/S2214-109X(17)30375-3.
20. Di Martino V, Lebray P, Myers RP, Pannier E, Paradis V, Charlotte F, et al. Progression of liver fibrosis in women infected with hepatitis C: long-term benefit of estrogen exposure. *Hepatology*. 2004;40(6):1426-33. Epub 2004/11/27. doi: 10.1002/hep.20463. PubMed PMID: 15565616.
21. Denniston MM, Klevens RM, McQuillan GM, Jiles RB. Awareness of infection, knowledge of hepatitis C, and medical follow-up among individuals testing positive for hepatitis C: National Health and Nutrition Examination Survey 2001-2008. *Hepatology*. 2012;55(6):1652-61. Epub 2012/01/04. doi: 10.1002/hep.25556. PubMed PMID: 22213025; PubMed Central PMCID: PMC4586034.
22. Observatory P. Hepatitis C Report 2017 [updated 07/26/17; cited 2017 08/20/17]. Available from: <http://polarisobservatory.org/polaris/hepC.htm>.
23. Krans EE, Zickmund SL, Rustgi VK, Park SY, Dunn SL, Schwarz EB. Screening and evaluation of hepatitis C virus infection in pregnant women on opioid maintenance therapy: A retrospective cohort study. *Substance abuse*. 2016;37(1):88-95. Epub 2015/11/17. doi: 10.1080/08897077.2015.1118720. PubMed PMID: 26569631; PubMed Central PMCID: PMC4827149.
24. Schackman BR, Gutkind S, Morgan JR, Leff JA, Behrends CN, Delucchi KL, et al. Cost-effectiveness of hepatitis C screening and treatment linkage intervention in US methadone maintenance treatment programs. *Drug Alcohol Depend*. 2018;185:411-20. Epub 2018/02/27. doi: 10.1016/j.drugalcdep.2017.11.031. PubMed PMID: 29477574; PubMed Central PMCID: PMC5889754.
25. Zuckerman A, Douglas A, Nwosu S, Choi L, Chastain C. Increasing success and evolving barriers in the hepatitis C cascade of care during the direct acting antiviral era. *PLoS ONE*. 2018;13(6):e0199174. doi: 10.1371/journal.pone.0199174.
26. Krans EE, Zickmund SL, Rustgi VK, Park SY, Dunn SL, Schwarz EB. Screening and evaluation of hepatitis C virus infection in pregnant women on opioid maintenance therapy: A retrospective cohort study. *Substance Abuse*. 2016;37(1):88-95. doi: 10.1080/08897077.2015.1118720.

27. Poynard T, Bedossa P, Opolon P. Natural history of liver fibrosis progression in patients with chronic hepatitis C. The OBSVIRC, METAVIR, CLINIVIR, and DOSVIRC groups. *Lancet*. 1997;349(9055):825-32. Epub 1997/03/22. PubMed PMID: 9121257.
28. World Health Organization W. Global Health Observatory - Life tables by country 2018 [updated 2018-04-20]. Available from: <http://apps.who.int/gho/data/view.main.60740?lang=en>.
29. van der Meer AJ, Veldt BJ, Feld JJ, Wedemeyer H, Dufour JF, Lammert F, et al. Association between sustained virological response and all-cause mortality among patients with chronic hepatitis C and advanced hepatic fibrosis. *Jama*. 2012;308(24):2584-93. Epub 2012/12/27. doi: 10.1001/jama.2012.144878. PubMed PMID: 23268517.
30. Morgan RL, Baack B, Smith BD, Yartel A, Pitasi M, Falck-Ytter Y. Eradication of hepatitis C virus infection and the development of hepatocellular carcinoma: a meta-analysis of observational studies. *Ann Intern Med*. 2013;158(5 Pt 1):329-37. Epub 2013/03/06. doi: 10.7326/0003-4819-158-5-201303050-00005. PubMed PMID: 23460056.
31. Razavi H, ElKhouri AC, Elbasha E, Estes C, Pasini K, Poynard T, et al. Chronic Hepatitis C Virus (HCV) Disease Burden and Cost in the United States. *Hepatology*. 2013;57(6):2164-70. doi: 10.1002/hep.26218. PubMed PMID: PMC3763475.
32. McAdam-Marx C, McGarry LJ, Hane CA, Biskupiak J, Deniz B, Brixner DI. All-cause and incremental per patient per year cost associated with chronic hepatitis C virus and associated liver complications in the United States: a managed care perspective. *Journal of managed care pharmacy : JMCP*. 2011;17(7):531-46. Epub 2011/08/30. doi: 10.18553/jmcp.2011.17.7.531. PubMed PMID: 21870894.
33. El Khouri AC, Klimack WK, Wallace C, Razavi H. Economic burden of hepatitis C-associated diseases in the United States. *J Viral Hepat*. 2012;19(3):153-60. Epub 2012/02/15. doi: 10.1111/j.1365-2893.2011.01563.x. PubMed PMID: 22329369.
34. U.S. Department of Health and Human Services CfMMS. Fee schedules.
35. Assoumou SA, Tasillo A, Leff JA, Schackman BR, Drainoni ML, Horsburgh CR, et al. Cost-Effectiveness of One-Time Hepatitis C Screening Strategies Among Adolescents and Young Adults in Primary Care Settings. *Clin Infect Dis*. 2018;66(3):376-84. Epub 2017/10/12. doi: 10.1093/cid/cix798. PubMed PMID: 29020317; PubMed Central PMCID: PMC5848253.
36. BusinessWire. Gilead Subsidiary to Launch Authorized Generics of Epclusa® (Sofosbuvir/Velpatasvir) and Harvoni® (Ledipasvir/Sofosbuvir) for the Treatment of Chronic Hepatitis C - List Price of Authorized Generics to Reflect Discounts in the System 2018 [updated 09/24/2018 11/11/2018]. Available from: <https://http://www.businesswire.com/news/home/20180924005499/en>.
37. Rein DB, Smith BD, Wittenborn JS, Lesesne SB, Wagner LD, Roblin DW, et al. The cost-effectiveness of birth-cohort screening for hepatitis C antibody in U.S. primary care settings. *Ann Intern Med*. 2012;156(4):263-70. Epub 2011/11/08. doi: 10.7326/0003-4819-156-4-201202210-00378. PubMed PMID: 22056542.
38. Fattovich G, Giustina G, Degos F, Tremolada F, Diodati G, Almasio P, et al. Morbidity and mortality in compensated cirrhosis type C: a retrospective follow-up study of 384 patients. *Gastroenterology*. 1997;112(2):463-72. Epub 1997/02/01. PubMed PMID: 9024300.

39. Salomon JA, Weinstein MC, Hammitt JK, Goldie SJ. Empirically calibrated model of hepatitis C virus infection in the United States. *Am J Epidemiol*. 2002;156(8):761-73. Epub 2002/10/09. PubMed PMID: 12370165.
40. Marfatia S, Gupta K, Mukherjee A, Mattoo V. Direct Medical Cost Associated With The Diagnosis and Treatment of Patients With Chronic Hepatitis-B In Three Large Metropolitan Cities In India - A Pilot Study. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research*. 2015;18(7):A581-2. Epub 2015/11/05. doi: 10.1016/j.jval.2015.09.1945. PubMed PMID: 26533268.
41. Jhaveri R, Broder T, Bhattacharya D, Peters MG, Kim AY, Jonas MM. Universal Screening of Pregnant Women for Hepatitis C: The Time Is Now. *Clin Infect Dis*. 2018;67(10):1493-7. doi: 10.1093/cid/ciy586.
42. Plunkett BA, Grobman WA. Routine hepatitis C virus screening in pregnancy: a cost-effectiveness analysis. *Am J Obstet Gynecol*. 2005;192(4):1153-61. Epub 2005/04/23. doi: 10.1016/j.ajog.2004.10.600. PubMed PMID: 15846195.
43. Selvapatt N, Ward T, Bailey H, Bennett H, Thorne C, See LM, et al. Is antenatal screening for hepatitis C virus cost-effective? A decade's experience at a London centre. *J Hepatol*. 2015;63(4):797-804. Epub 2015/05/31. doi: 10.1016/j.jhep.2015.05.015. PubMed PMID: 26024832.
44. He T, Li K, Roberts MS, Spaulding AC, Ayer T, Grefenstette JJ, et al. Prevention of Hepatitis C by Screening and Treatment in U.S. Prisons. *Ann Intern Med*. 2016;164(2):84-92. Epub 2015/11/26. doi: 10.7326/m15-0617. PubMed PMID: 26595252; PubMed Central PMCID: PMC4854298.
45. Eckman MH, Ward JW, Sherman KE. Cost Effectiveness of Universal Screening for HCV Infection in the Era of Direct-Acting, Pangenotypic Treatment Regimens. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association*. 2018. Epub 2018/09/12. doi: 10.1016/j.cgh.2018.08.080. PubMed PMID: 30201597.
46. Kushner T, Cohen J, Tien PC, Terrault NA. Evaluating Women's Preferences for Hepatitis C Treatment During Pregnancy. *Hepatology communications*. 2018;2(11):1306-10. doi: 10.1002/hep4.1264. PubMed PMID: 30411077.
47. Martin NK, Vickerman P, Dore GJ, Grebely J, Miners A, Cairns J, et al. Prioritization of HCV treatment in the direct-acting antiviral era: An economic evaluation. *J Hepatol*. 2016;65(1):17-25. Epub 2016/02/13. doi: 10.1016/j.jhep.2016.02.007. PubMed PMID: 26867489; PubMed Central PMCID: PMC4914770.
48. Salomon JA, Weinstein MC, Hammitt JK, Goldie SJ. Cost-effectiveness of treatment for chronic hepatitis C infection in an evolving patient population. *Jama*. 2003;290(2):228-37. Epub 2003/07/10. doi: 10.1001/jama.290.2.228. PubMed PMID: 12851278.
49. Bruno S, Zuin M, Crosignani A, Rossi S, Zadra F, Roffi L, et al. Predicting mortality risk in patients with compensated HCV-induced cirrhosis: a long-term prospective study. *Am J Gastroenterol*. 2009;104(5):1147-58. Epub 2009/04/09. doi: 10.1038/ajg.2009.31. PubMed PMID: 19352340.
50. Barocas JA, Tasillo A, Eftekhari Yazdi G, Wang J, Vellozzi C, Hariri S, et al. Population level outcomes and cost-effectiveness of expanding the recommendation for age-based hepatitis C testing in the United States. *Clin Infect Dis*. 2018. Epub 2018/02/09. doi: 10.1093/cid/ciy098. PubMed PMID: 29420742.

51. Montenovo MI, Dick AA, Hansen RN. Donor hepatitis C sero-status does not impact survival in liver transplantation. *Annals of transplantation*. 2015;20:44-50. Epub 2015/01/23. doi: 10.12659/aot.892530. PubMed PMID: 25608491.
52. Services USDoHaHSCfM, Medicaid CfM. Clinical diagnostic laboratory fee schedule.
53. Thein HH, Krahn M, Kaldor JM, Dore GJ. Estimation of utilities for chronic hepatitis C from SF-36 scores. *Am J Gastroenterol*. 2005;100(3):643-51. Epub 2005/03/04. doi: 10.1111/j.1572-0241.2005.40976.x. PubMed PMID: 15743364.
54. Chong CA, Gulamhussein A, Heathcote EJ, Lilly L, Sherman M, Naglie G, et al. Health-state utilities and quality of life in hepatitis C patients. *Am J Gastroenterol*. 2003;98(3):630-8. Epub 2003/03/26. PubMed PMID: 12650799.
55. Wright M, Grieve R, Roberts J, Main J, Thomas HC. Health benefits of antiviral therapy for mild chronic hepatitis C: randomised controlled trial and economic evaluation. *Health technology assessment (Winchester, England)*. 2006;10(21):1-113, iii. Epub 2006/06/06. PubMed PMID: 16750059.

TABLES

Table 1. Model parameters inputs and sources. DC: decompensated cirrhosis, HCC: hepatocellular carcinoma, PWID: people who inject drugs, SVR: sustained viral response.

State Transitions	HCV Stage	Mean sampled value (2.5%-97.5% quantiles)	Sampling distribution	Source
HCV chronic prevalence among pregnant women		0.73% (0.71- 0.75%)	Uniform Range: 0.709-0.751	(2)
HCV antibody prevalence among pregnant women		1.10% (1.02 -1.20%)		Calculated based on spontaneous clearance rate
Proportion who spontaneously clear their acute infection		34% (30–38%)	Uniform Range: 0.3-0.38	(9)
Annual loss to follow-up rates after HCV diagnosis		12% (7-17%)	Uniform Range: 0.07-0.17	(26)
Proportion HCV-infected pregnant women previously diagnosed and linked to care		18% (10-25%)	Uniform Range: 0.1-0.26	(21, 22) see text
Background testing and linkage rate per year		5% (2.6-7.4%)	Uniform Range: 2.5-7.5	Assuming an annual testing rate of 10%/year with 50% linked to care (24)
HCV chronic prevalence among PWID (%)		52% (44–59%)	Uniform Range: 43-60	(18, 19)
Liver disease stage transition rate per year	F0 to F1	0.1125 (0.996-0.1261)	Beta (251.2107 1984.813)	(27)
	F1 to F2	0.1125 (0.996-0.1261)	Beta (251.2107 1984.813)	(27)
	F2 to F3	0.1125 (0.996-0.1261)	Beta (251.2107 1984.813)	(27)
	F3 to F4	0.1125 (0.996-0.1261)	Beta (251.2107 1984.813)	(27)
	F4 to DC	0.0406 (0.0312-0.0520)	Beta (58.49116 1380.788)	(38, 39, 48)
	F4 to HCC	0.0212 (0.0163-0.0276)	Beta (52.83443, 2417.472)	(38, 39, 48)
	DC to HCC	0.0141 (0.0016-0.0395)	Beta (1.9326, 136.1074)	(38)
	DC/HCC to transplant	0.0313 (0.0014-0.1077)	Beta (1.152814, 36.03474)	(37, 38, 48)

State Transitions	HCV Stage	Mean sampled value (2.5%-97.5% quantiles)	Sampling distribution	Source
Proportion who achieve SVR		0.90	Uniform Range: 0.85-0.95	(3)
Liver-related death rate per year	F4	0.0324 (0.01716- 0.05234)	Beta (12.44677 371.1121)	(49)
	DC	0.2210 (0.1207- 0.3414)	Beta (11.61594 40.93614)	(49)
	HCC	0.2210 (0.1207- 0.3414)	Beta (11.61594 40.93614)	(49, 50)
	Transplant year 1	0.1715 (0.1378- 0.2081)	Beta (75.4499 364.4907)	(51)
	Post transplant (year 2+)	0.0353 (0.0288- 0.0425)	Beta (97.65551 2665.93)	(51)
Annual background mortality rate	Varies by age			(2, 28) WHO lifetable, Assuming age 27 at pregnancy
Relative risk of progression if SVR compared to no SVR	F4 to DC	0.07 (0.03-0.2)	Lognormal (5.6356,2.43983)	(29)
	F4 to HCC	0.23 (0.16-0.35)	Lognormal (-3.37754,1.9534)	(29, 30)
	DC to HCC	1	-	
HCV fibrosis distribution among HCV diagnosed women	F0	0.16		(20)
	F1	0.43		
	F2	0.21		
	F3	0.10		
	F4	0.10		
Cost (all costs inflated to USD\$ 2018 (34))				
Annual costs for non-treatment medical expenses among HCV- infected patients	F0-F3	\$511 (\$304-734)	Uniform +/- 50% point estimate	(31-33)
	F4	\$2,898 (\$2,009-3,786)	Uniform +/- 50% point estimate	
	DC	\$34,319 (\$32,352-36,330)	Uniform +/- 50% point	

State Transitions	HCV Stage	Mean sampled value (2.5%-97.5% quantiles)	Sampling distribution	Source
			estimate	
	HCC	\$54,741 (\$49,302-60,014)	Uniform +/- 50% point estimate	
	Liver transplant Y1	\$225,320 (\$119,270-330,260)	Uniform +/- 50% point estimate	(32)
	Liver transplant following years	\$55196 (\$28773-81181)	Uniform +/- 50% point estimate	(32)
HCV Antibody test (including consultation)		\$39	--	(50, 52)
HCV RNA test (including consultation)		\$52	--	(50, 52)
Liver elastography		<u>\$130</u>	--	(50, 52)
HCV antiviral therapy drug cost only per treatment course		\$25,000	--	(36) and glecaprevir/pib rentasvir wholesale acquisition cost
Treatment delivery costs per course		\$1,249 (\$676-1,853)	Uniform +/- 50% point estimate	(3) Table S1
Health Utilities				
Uninfected		1		(37)
HCV-infected patients	F0	0.93 (0.83-1)	Beta (59.95413,4.512676)	(37, 53, 54)
	F1, F2	0.86 (0.78-0.94)	Beta (29.92649,4.871755)	
	F3	0.83 (0.78-0.89)	Beta (12.30437,2.520171)	
	F4	0.81 (0.68-0.89)	Beta (41.6698,9.774397)	
	DC	0.70 (0.56-0.79)	Beta (39.8121,17.06233)	
	HCC	0.67 (0.56-0.78)	Beta (35.508,17.48901)	
	Post-Transplant	0.71 (0.69-0.79)	Beta (7.612184,3.109202)	
Incremental increase in health utility upon SVR		0.05		(55)

Table 2. Cost-effectiveness results of HCV antenatal versus background screening. ICER:
Incremental Cost-effectiveness Ratio. QALYs quality adjusted life years.

Scenario	Cost per person (2018 USD \$) Mean and 2.5- 97.5% Intervals	Mean QALYs per person. Mean and 2.5-97.5% Intervals	Incremental Cost per person. Mean and 2.5-97.5% Intervals	Incremental QALYs per person. Mean and 2.5-97.5% Intervals	Mean ICER (USD\$/QALY gained)
Background screening	921 (443-1397)	25.312 (25.297-25.325)			
Universal antenatal screening and treatment after pregnancy regardless of fibrosis stage	975 (442-1510)	25.331 (25.315-25.343)	53 (-102-175)	0.019 (0.010-0.028)	2826

FIGURE

Figure 1: Impact of HCV chronic prevalence among pregnant women (x axis) on the incremental cost-effectiveness ratio (ICER, y axis) of screening pregnant woman compared to background risk-based screening. Willingness to pay threshold of \$50,000/QALY denoted by a horizontal dashed line.

